Dynamic adaptation of the peripheral adaptation to cold exposure

Cheung, S.S.; Daanen, H.A.M.

published in
Microcirculation
2012

DOI (link to publisher)
10.1111/j.1549-8719.2011.00126.x

document version
Publisher's PDF, also known as Version of record

Microcirculation
The Official Journal of the Microcirculatory Society, Inc.

DOI:10.1111/j.1549-8719.2011.00126.x

Invited Review

Dynamic Adaptation of the Peripheral Circulation to Cold Exposure

STEPHEN S. CHEUNG,* AND HEIN A.M. DAANEN†

*Environmental Ergonomics Laboratory, Department of Kinesiology, Brock University, St. Catharines, ON, Canada; †TNO Behavioural and Societal Sciences, Human Performance Expertise Group, Soesterberg, and MOVE Research Group, Faculty of Human Movement Sciences, VU University, Amsterdam, The Netherlands

Address for correspondence: Stephen S. Cheung, Ph.D., Department of Kinesiology, Brock University, 500 Glenridge Avenue, St. Catharines, ON, L2S-3A1, Canada. *E-mail:* stephen.cheung@brocku.ca

Received 16 May 2011; accepted 14 August 2011.

ABSTRACT

Humans residing or working in cold environments exhibit a stronger cold-induced vasodilation (CIVD) reaction in the peripheral microvasculature than those living in warm regions of the world, leading to a general assumption that thermal responses to local cold exposure can be systematically improved by natural acclimatization or specific acclimation. However, it remains unclear whether this improved tolerance is actually due to systematic acclimatization, or alternately due to the genetic predisposition or self-selection for such occupations. Longitudinal studies of repeated extremity exposure to cold demonstrate only ambiguous adaptive responses. In field studies, general cold acclimation may lead to increased sympathetic activity that results in reduced finger blood flow. Laboratory studies offer more control over confounding parameters, but in most studies, no consistent changes in peripheral blood flow occur even after repeated exposure for several weeks. Most studies are performed on a limited amount of subjects only, and the variability of the CIVD response demands more subjects to obtain significant results. This review systematically surveys the trainability of CIVD, concluding that repeated local cold exposure does not alter circulatory dynamics in the peripheries, and that humans remain at risk of cold injuries even after extended stays in cold environments.

Key words: fingers, toes, cold-induced vasodilation, cold exposure, cold injury, adaptation

Abbreviations used: AVA, arterio-venous anastomoses; CIVD, cold-induced vasodilation; CON, control group; EXP, experimental group; NE, norepinephrine; NO, nitric oxide; RIF, resistance index of frostbite; SCUBA, self-contained underwater breathing apparatus; T_{mean}, mean finger skin temperature; T_{min}, minimum finger skin temperature; T_{nadir}, nadir finger skin temperature; T_{peak}, peak finger skin temperature.

Please cite this paper as: Cheung and Daanen (2012). Dynamic Adaptation of the Peripheral Circulation to Cold Exposure. *Microcirculation* **19**(1), 65–77.

INTRODUCTION

Circulatory flow in the extremities adjusts rapidly and dynamically to cold exposure and also to the thermal state of the body [26]. Shortly upon exposure to cold environments, a sympathetically mediated vasoconstriction results in reduced blood flow to the peripheries in favor of a central pooling of blood in the torso and deep body core. Due to the vasoconstriction of the peripheral microvasculature and the high surface area-to-volume ratio, the skin temperature of the fingers and toes tends to rapidly and exponentially decrease to a level approaching that of the ambient environment. Prolonged cooling increases the tonus of the precapillary sphincters, leading to reduced nutritional blood flow; this in turn may lead to tissue damage and even necrosis—commonly observed in nonfreezing cold injuries. Continued cold exposure and vasoconstriction can also lead to cold injuries such as frostbite from cell temperature dropping below the point of freezing and crystallization [74].

Despite an overall drive for vasoconstriction in the cold, a common observation is that, after a brief period of lowered skin temperature, a seemingly paradoxical and temporary increase in blood flow and rewarming occurs in the toes and fingertips. During these episodes, skin temperature can rise by as much as 10°C, and this fall and rise can occur repeatedly in a cyclic fashion. This pattern of periodic warming was first reported by Lewis [49], and he labeled it the "hunting response" for its apparent oscillatory pattern—this response has also been termed the CIVD phenomenon [15]. In addition to the fingers and toes, CIVD has been observed in various regions of the body, including the face [8] and feet [38].

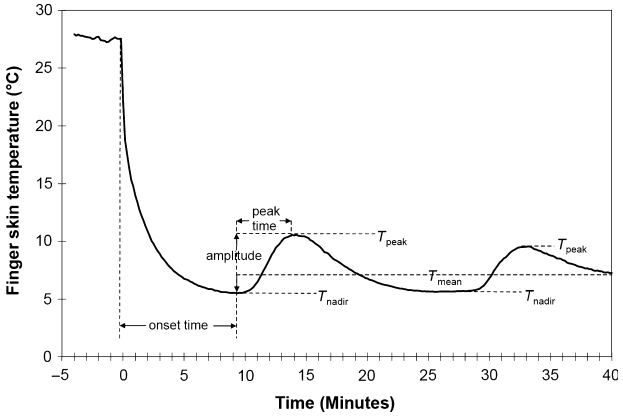

Figure 1. General schematic of typical CIVD responses in finger skin temperature (°C) during 40 minutes of immersion in cold water. T_{min} and T_{max} equal T_{nadir} and T_{peak} of the highest CIVD wave.

A stylized "classic" CIVD response is provided in Figure 1, demonstrating the typical responses and measures used to quantify CIVD. In all supposed mechanisms of CIVD, the AVAs are thought to play an essential role, with a relaxation of the AVA that in turn causes an increase in local blood flow and tissue temperature at the extremity. Indirect evidence that AVAs are involved in CIVD is derived from the finding that CIVD occurs mainly at the AVA locations [29]. Another important indirect argument for the involvement of AVAs is that capillary blood flow is insufficient to explain the magnitude of heat loss that is observed during CIVD [73]. Bergersen *et al.* [7] used different Doppler techniques to provide more direct evidence that AVAs are actively involved in CIVD.

While the mechanisms underlying CIVD remain unclear, understanding the nature of CIVD and its potential adaptation over time is of important occupational and clinical relevance. Because of the elevated extremity blood flow and temperature, CIVD has generally been presumed to provide a protective function by maintaining local tissue integrity and minimizing the risk of cold injuries. Through this enhancement of finger temperature, it is also presumed that CIVD can improve manual dexterity in the cold, although Geurts *et al.* [33] found no relationship between finger temperature and twitch characteristics of the first dorsal interosseous muscle. CIVD is often not observed or minimal in individuals with Raynaud's syndrome [41], which is characterized by extreme vasospasms and ischemia in the digits triggered by cold or emotional stress [6]. However, repeated exposure of the hands or feet to cold water generally decreases perceptual sensations of discomfort. In a study on classical behavioral conditioning, Jobe *et al.* [42] exposed Raynaud's individuals to whole body cold while the hand was immersed in warm water, thus conditioning the individuals to associate a cold body with warm fingers, ultimately enhancing finger temperatures. Overall, the relationship between attenuated perceptual discomfort from adaptation and the triggering of vasospasms remains largely unexplored.

Chief amongst the proposed clinical benefits of an improved CIVD response is a potential reduction in the risk for nonfreezing and freezing cold injuries, especially in occupational (e.g., military, utility workers in the cold) and recreational (e.g., mountaineering) settings. Daanen and van der Struijs [20] provided some epidemiological support when testing a group of military marines for CIVD responses prior to Arctic deployment. Retrospectively, the eleven soldiers who acquired cold injuries had a reduced CIVD response compared with the other 195 tested soldiers without acquired cold injuries during deployment (see Figure 2). While CIVD may indeed prevent the occurrence of cold injuries, this is balanced by an increased heat loss that enhances the risk for whole-body hypothermia; when mild hypothermia and local cold exposure of the extremities coincide, prevention of further body cooling becomes the dominant mechanism and CIVD decreases [16]. In practical work settings, however, humans are generally well dressed to maintain body core temperature, but have to expose the hands to the cold to perform tasks. In those field settings, an enhanced CIVD response may be beneficial, leading researchers to explore how CIVD may be stimulated or enhanced.

Current consensus appears to be that CIVD is a trainable response that can be systematically manipulated and improved through repeated local cold exposure, as outlined by Astrand's classic *Textbook of Work Physiology* [5]:

"When a person, whether an arctic native or otherwise, allows his or her hands to be repeatedly exposed to cold for about ½ h daily for a few weeks, this cold stress

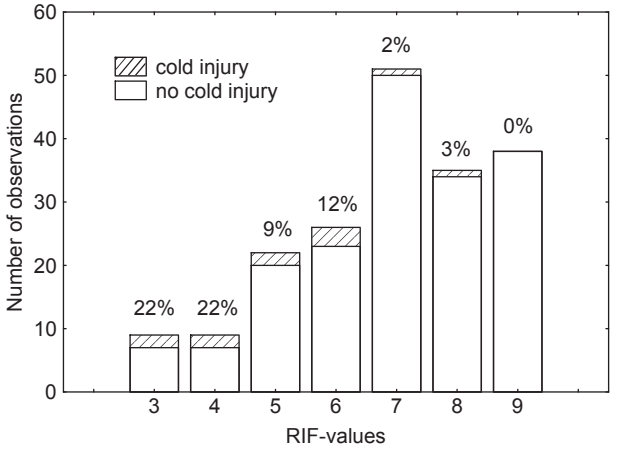

Figure 2. RIF values for 11 subjects who suffered cold injuries compared with the other 179 measured subjects. The percentages denote the percentage of cold injuries that occurred for each RIF value. An RIF of 3–4 is classified as a weak reaction, 5–7 as average, and 8–9 as strong [75]. From Daanen and van der Struijs [19] with permission.

increases the blood flow through the hands, so that they remain warmer and are not so apt to become numb when exposed to cold. This is termed local acclimatization to cold. Although it inevitably will cause a greater amount of heat to be lost from the hands, it will improve the ability of the hands and fingers to perform work of a precise nature in the cold."

Despite this apparent consensus, a closer examination of the CIVD trainability literature appears to be warranted, as there remain major gaps in knowledge concerning the trainability of CIVD. Historically, cross-sectional population studies comparing cold-adapted/native individuals with control groups suggest that the CIVD reaction can be more pronounced in the cold adapted/native individuals. However, shorter acclimatization protocols have argued both for and against changes in thermal responses. Furthermore, recent laboratory-based acclimation studies have largely been unable to elicit significant changes in thermal or CIVD responses. Therefore, in this review, we aimed to combine the results of field and laboratory studies to fully evaluate the trainability of CIVD, with the goal of determining whether humans can be physiologically trained to decrease their risk of local cold injuries.

METHODOLOGICAL ISSUES IN CIVD RESEARCH

In the process of surveying the CIVD literature, one major caveat is the lack of consensus in definition and protocols, making it very difficult to compare results across studies. As seen in Figure 1, many parameters are used to quantify CIVD, and studies may report improved CIVD simply from a change in a single parameter, with other parameters either not significant or not reported. At its most basic, no standardized definition for a rise in digit skin temperature that constitutes a CIVD event exists, with some studies depending on a deflection of skin temperature from a baseline [1,16,49], through to temperature increases ranging from 0.5°C to 4.0°C as a CIVD threshold [28,36]. Similar variability exists in quantifying what is actually meant by an improved thermal response across studies, which can consist of factors, such as more numerous CIVD events, higher mean or minimum digit temperatures, or more rapid onset times for CIVD [15]. To overcome these methodological differences, we carefully read the methodology of each study and determined to report the parameters that are most common for CIVD research like onset time and mean, minimum, maximum finger/toe temperatures.

Another example of methodological variability across studies is the use of either skin blood flow or skin temperature, each of which may be measured with different types of sensors at different sites, as generally interchangeable methods for measuring CIVD. While the transposition of blood flow and skin temperature may appear intuitive, little direct evidence exists. Shitzer *et al.* [69] modeled and experimentally validated the relationship between blood perfusion in the fingertips during cold exposure with finger skin temperature, whereas Daanen [14] reported that skin perfusion preceded the temperature response by 112 ± 72 seconds with a cross-correlation coefficient of 0.76 ± 0.14. Figure 3 illustrates the many different responses possible from cold exposure, further making quantification of CIVD difficult.

For research in this field to advance, it seems critical that basic standardized definitions and protocols be adopted to maximize the integration of research. O'Brien's [59] study on the reproducibility of CIVD may provide a starting point for standardization of ambient and individual factors; a number of individual factors were standardized in a study on the reproducibility of CIVD, including circadian rhythm, pre-test nutrition, posture, site of sensor placement, and pre-immersion in warm water to normalize vasodilation. Other experimental factors may need to be controlled, especially depth of digit or limb immersion [68], along with ambient or core temperatures due to the strong relationship between body temperature and CIVD response [19,25], and the demonstration that facial protection improved finger temperature and thermal comfort during whole-body cold exposure [60]. Such standardization may be difficult in field studies, such as in mountaineers at high altitudes, but at the very least, the individual factors should be controlled as best as possible and reported.

POPULATION STUDIES

Ethnic Differences

Given the basic assumption that ethnic groups residing in Arctic areas have more general and local cold exposure than ethnic groups who reside in tropical areas, this may have resulted in genetic or functional adaptations over the course of their ancestry. Therefore, it is worthwhile to look at racial differences in local responses to cold. Many of the early studies on cold tolerance employed a cross-sectional approach comparing nonadapted controls with a population living or working in cold environments. Alternatively, if the control group could be drawn from individuals of similar ethnicity, it can be assumed that the primary difference is in environmental exposure rather than in genetic differences. In support of CIVD being a protective response, humans living in or native to a cold environment seems to have enhanced CIVD, marked by shortened onset times and higher amplitudes, compared with tropical or nonadapted individuals. For example, Arctic natives such as Inuit and Lapps generally have higher mean finger temperatures and CIVD responses compared with control pop-

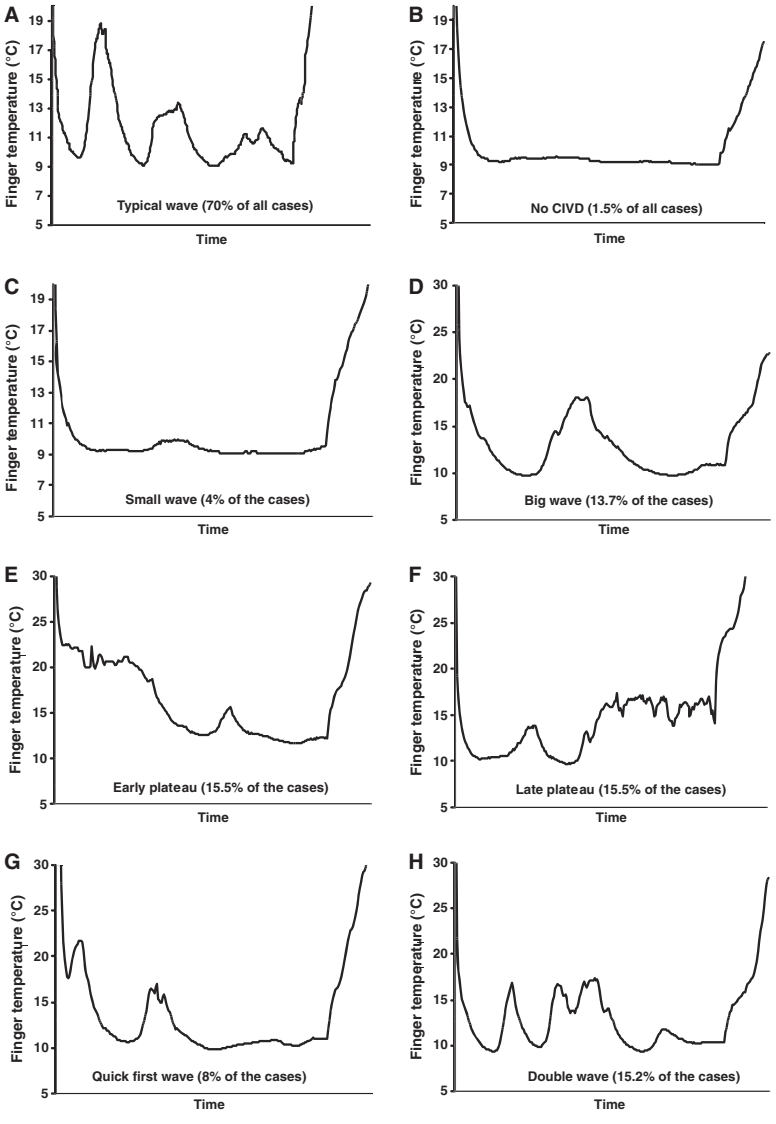

Figure 3. Multiple thermal responses in the fingers are possible that deviate from the classic cyclical pattern of rising and falling skin temperature associated with CIVD. Such disparity in potential responses can make it difficult to properly categorize CIVD prevalence and also the quantification of CIVD parameters outlined in Figure 1. All graphs are for 30 min of immersion and 5 min of recovery. Reproduced with permission from Mekjavic *et al.* [54].

ulations from more temperate regions [12,45,56]. Negroid subjects are known to have lower finger skin temperatures during CIVD than Caucasians [54]. Leblanc *et al.* [47] observed no differences in skin thickness or cell size between skin biopsies of fishermen and controls; however, the fishing group had a greater number of mast cells in the skin. Mast cells are present in several types of tissues, and contain many granules rich in histamine; H2 histamine receptors are located in smooth muscle cells, and cause a strong vasodilation when stimulated. Again, it is not known if these differences were inherited or acquired.

Some ethnic groups continued to be exposed to local and whole body cold for centuries, like the Inuit, whereas other ethnic groups were mainly exposed to heat. Early population-based research demonstrated that Arctic residents have a better CIVD response than non-Arctic residents [12,45,56]. Even though the fingers are relatively shorter and thicker for people living close to the poles [2,48], providing less biophysical [62] surface area for heat exchange, the fingers nevertheless seem to be able to lose more heat to the environment when exposed to severe cold. Locations where CIVD is observed coincide with the presence of AVAs in the human skin [7]. These AVAs contain alpha-2 receptors and are under powerful sympathetic control; when CIVD occurs, the strong muscle wall of the AVA suddenly relaxes. Hale and Burch [39] reported that

AVAs form when there is a higher need for blood flow in the finger. However, the magnitude of this response is very small: 95% of the AVAs remain unchanged and the stimulus for AVA formation has to be severe, for instance, strong ischemia followed by hyperemia. Therefore, the relative contribution of new AVA formation to CIVD adaptation is estimated to be small. However, while speculative, in thick fingers, it may take more time before the AVA reaches the critical temperature below which CIVD is evoked. Also, the sympathetic response to local cold is probably blunted for Arctic residents, causing higher blood flows and mean finger temperatures during local cold exposure.

As a caveat, even within a particular nationality, dramatic differences in thermal responses may exist. Mathew *et al.* [52] compared four groups of Indian natives in their CIVD response to local hand exposure to 4°C water. The groups studied included southern natives with little to no cold experience, northern Indians, Gurkhas, and high-altitude (>3500 m) natives. When tested at both low and high altitudes, heat output in the hands of the high-altitude natives was significantly higher, and that in the hands of the southern Indians lower, than any other ethnic groups. Such observations highlight the importance of careful matching when employing a control group in cross-sectional comparison.

Local Cold Acclimatization

Enhancement in thermal response of the hands has been seen in individuals working in environments with repeated local cold exposures, such as fish filleters [58]. Arguably, the occupation of fish filleting versus technical staff in this study would feature a direct case of local cold exposure as the primary population difference. However, population studies targeting specific occupations, such as fishers, mountaineers, and indeed laboratory volunteers, may still suffer from the potential for self-selection for such occupations. It is not unlikely that only subjects with high finger blood flow or CIVD response opt for the job of fish filleter. In contrast, individuals who experience severe negative physiological or psychological reactions to local cold exposure are likely to actively disqualify themselves from such occupations or as volunteers for experiments. Therefore, the observed changes may not be due to an acute or chronic acclimatization response, but rather due to pre-existing innate physiological differences. While fish filleters are mainly exposed to local cold, fishermen experience both general and local cold exposure. Therefore, the differences in CIVD between fishermen and controls are also ambiguous. Leblanc *et al.* [47] and Krog *et al.* [45] found enhanced CIVD in fishermen, while Hellstrom and Andersen [40] observed no differences.

Conclusions Regarding Population Studies

While useful in delineating gross differences in CIVD response, one inherent difficulty in cross-sectional population studies is accounting for the true differences in cold exposure across two populations. For example, groups may differ in both local and general, whole-body cold exposure; this becomes problematic because whole body thermal status is known to affect the CIVD response [16,66]. Another limitation of such studies is that, by comparing two distinct groups, little information is provided on the time course or mechanism of any adaptations to cold, or indeed on the ability of CIVD to be trained and improved.

LONGITUDINAL FIELD STUDIES

The most ecologically valid approach to determining the trainability of the CIVD response is to track individuals before, throughout, and after a prolonged period of natural exposure to cold stress. However, from a methodological and research design perspective, this approach is difficult to control, and it is not easy to isolate individual factors and mechanisms that can contribute to local thermal adaptation of the extremities. For example, it can be difficult to accurately quantify the duration and intensity of both whole-body and local cold exposure, such that results from field studies present equivocal evidence for adaptation. Table 1 summarizes a number of the existing field and laboratory studies on CIVD trainability.

A number of studies suggest minimal adaptation even from occupations experiencing extensive local and/or general exposure to cold. One such study tracked a group of SCUBA divers stationed with the British Antarctic Survey for a year, with monthly laboratory immersions of the index finger into ice water [11]. Compared with a control group of nondiving Survey members, no significant differences were reported in CIVD response between the groups over the study period, nor were there differences in subjective pain response. While one potential explanation may have been that an overall drop in core temperature during diving blunted the potential CIVD response, an earlier study on the same population reported that rectal temperature during diving did not decrease below 36.0°C, even though finger temperature decreased to 10°C over the approximate 30-minute dives [10]. Therefore, it must be concluded that significant peripheral cooling repeatedly occurred in the diving group over the course of the year, but that such repeated local cold exposure did not significantly affect core temperature nor enhance CIVD response. Furthering the lack of response, Livingstone [50] and Livingstone *et al.* [51] reported lower mean finger temperatures in groups of Canadian soldiers upon immersion of the middle finger into ice water following a two-week

Table 1. Overview of CIVD onset time (min), amplitude (°C), mean finger skin temperature (T_{mean}. °C), and minimum finger skin temperature of the first wave (nadir temperature) (T_{min}, °C) in 16 selected field or laboratory studies

		Onset time				Amplitude				T_{mean}				T_{min}			
		EXP		CON		EXP		CON		EXP		CON		EXP		CON	
Study	*N*	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Daanen *et al.* 2007	8	3.0 (0.0)	2.5 (0.5)	3.0 (0.0)	2.5 (0.5)					10.1 (3.8)	7.1 (3.1)	11.1 (3.5)	6.9 (2.9)	4.5 (3.9)	3.8 (2.5)	5.7 (4.1)	6.9 (2.9)
Dobnikar 2007	8		5.9 (8.4)				3.5 (1.8)				11.5 (1.6)				8.7 (0.7)		
Adams and Smith 1962	5		7.0 (0.2)		8.0 (0.2)												
Geurts *et al.* 2005a	10	7.4 (2.9)	12.3 (6.4)	8.9 (4.4)	9.6 (4.1)	5.3 (3.2)	2.5 (2.1)	3.0 (3.0)	3.0 (2.9)	14.2 (1.9)	11.7 (1.4)	12.1 (1.5)	11.5 (1.3)	10.6 (1.2)	9.3 (0.8)	9.2 (0.5)	9.3 (0.8)
Geurts *et al.* 2005b	12		17.3 (3.3)				3.8 (2.6)				14.4 (4.4)				9.5 (1.1)		
Geurts *et al.* 2006a	10	10.7 (4.2)	8.3 (3.7)	13.5 (8.4)	11.3 (6.8)	6.5 (3.8)	6.3 (3.0)	5.9 (6.3)	6.4 (6.8)	12.4 (2.8)	15.0 (3.0)			8.7 (0.7)	10.1 (1.3)		
Geurts *et al.* 2006b	11		15.4 (9.4)				2.7 (3.2)			16.2 (5.2)	18.8 (5.8)			10.9 (3.4)	12.8 (4.2)		
Yoshimura and Iida 1950	100									5.4 (1.5)							
Glaser and Whittow 1957	6									11.3 (1.5)	8.1 (0.4)						
Daanen and van Ruiten 2000	5		10.4 (9.4)		9.9 (4.0)		6.3 (2.9)		6.9 (4.3)		5.0 (1.9)		5.2 (2.5)		0.6 (0.4)		0.8 (1.0)
Reynolds *et al.* 2007	10		13.6 (5.4)				3.1 (1.7)										
O'Brien 2005	21			4.5 (1.0)								7.1 (0.9)				5.0 (0.8)	
Felicijan *et al.* 2008	9	6.5 (4.4)	6.0 (5.4)	5.6 (2.8)	8.0 (4.6)	7.0 (4.3)	8.1 (3.4)	6.3 (4.0)	6.1 (4.4)	16.1 (5.0)	17.0 (4.0)	13.9 (1.5)	14.3 (3.7)	12.7 (4.2)	14.3 (3.7)	11.9 (1.1)	11.7 (2.1)
Mekjavic *et al.* 2008	9									12.7 (2.8)	10.8 (0.9)	12.6 (1.2)	10.8 (0.8)			9.9 (1.1)	9.0 (0.5)
Nelms and Soper 1961	11		4.5 (1.6)		9.9 (2.6)												
Sendowski *et al.* 1997	20		5.9 (1.4)								15.9 (4.3)				9.7 (4.3)		

The experimental group (EXP) consisted of subjects of which the extremities were repeatedly exposed to cold. The control group (CON) concerned the nontrained group. In the Nelms and Soper study, the experimental group consisted of fish filleters; in the Felicijan study, the subjects were exposed to hypoxia instead of cold. The pre-test was performed before the intervention and the post-test immediately afterward. Glaser and Whittow only had 1 minute cold water immersions; the remaining studies employed time intervals of 30 minutes or more. Values are shown as a mean with standard deviation between parentheses.

Arctic expedition. However, one potential caveat in interpreting these studies, especially with the Canadian soldiers, is that the subjects were already living in winter environments, and may have experienced natural cold acclimatization and therefore limited further potential for adaptation.

Other literature suggests that field acclimatization is indeed possible. Tropical inhabitants—soldiers from the plains of India—exhibited an improved peripheral blood flow and CIVD response after seven weeks of exposure to the Arctic environment [63], but this remained below the level found in Arctic natives, and suggests that full adaptation requires much longer exposure periods.

Based on field acclimation studies, one intriguing possibility is that hypoxic exposure itself, irrespective of cold exposure, potentiates CIVD response and local thermal response to cold. With acute cold exposure in a laboratory setting, Simmons *et al.* [70–72] studied the effect of hypoxia on cutaneous vascular conductance during cold exposure. Data from these three studies are mixed, suggesting both increased and decreased cutaneous vasoconstriction in the forearm. However, further improvements in CIVD responses from hypoxic exposure may be possible even in those with presumably some degree of cold acclimatization or self-selection for cold. A subgrouping of peripheral cold adaptation studies has explored responses in alpinists over the course of expeditions at altitude. Daanen and van Ruiten [21] investigated if repeated finger cold water immersions at high altitude (4350 m) improved the CIVD response and observed no improvement in seven days. This was in contrast to the same study observing some improvement in mean finger temperature when subjects were acclimatized to high altitude (>5100 m) over 45 days. Therefore, a threshold for acclimatization duration may exist at altitude, as Mathew *et al.* [53] and Purkayastha *et al.* [64] reported CIVD enhancement within a time span of three weeks at altitude. Recently, Felicijan *et al.* [23] tested highly experienced (>20 years) Slovenian alpinists before and following a three-week high-altitude mountaineering expedition. Compared with a group of Slovenian non-mountaineering controls, CIVD was more pronounced in the toes pre-expedition, and the CIVD response was further enhanced in both the fingers and toes of the alpinists post-expedition. Amon [3] recently confirmed these observations in a laboratory study in which nine subjects were sleeping high and training low for 28 days without cold exposure; in particular, the number of CIVD waves increased. Overall, it seems that prolonged exposure to altitude may improve CIVD, and that a threshold exposure duration in excess of one week and close to three weeks or longer is required for significant adaptation.

Conclusions Regarding Field Studies

Longitudinal acclimatization studies, where a subject group is naturally exposed to cold for a prolonged period and tested for CIVD response, have to date presented equivocal results. However, studies in which local extremity cold water immersion was combined with altitude exposure for a prolonged period exceeding a week seem to yield positive results on CIVD. Such acclimatization studies can be logistically difficult to execute, due to the requirement to track subjects over a prolonged period of time and possibly in different geographical settings. Similar to population studies, another inherent problem in research design remains direct quantification of the level of actual cold exposure over the course of the acclimatization protocol, and the partitioning of local versus whole body exposure. Some longitudinal studies also lack a control group, making it difficult to assess the true environmental effect of exposure. Nevertheless, longitudinal studies can provide the best path for quantifying the potential extent for CIVD trainability in humans.

LABORATORY STUDIES

To increase methodological control over field studies, another option is to perform laboratory acclimation studies. The advantage of laboratory-based studies is the ability to isolate individual factors that may contribute to CIVD, such as duration and intensity of local and/or whole-body thermal stress. Studies on adaptation using this approach were performed extensively in the 1950s and 1960s, remained dormant for several decades, and have received renewed interest over the first decade of this century. The general trend of these studies suggests that laboratory acclimation is difficult to achieve without an intense and extensive protocol, and also that a greater potential for adaptation exists in the fingers compared with the toes.

Early Studies

Research in the 1950s and 1960s reveal no clear picture of the potential trainability of the CIVD response. One of the earliest laboratory acclimation studies is that of Yoshimura and Iida [77]. Five subjects immersed their middle finger in ice water every two or four days for a month. The CIVD response hardly changed; RIF, and index integrating onset time, average finger skin temperature, and minimal finger skin temperature during immersion of a single finger in ice water, was within 1 point (scale ranged from 3 to 9 and anchored to a norm of 6 based on a cohort of Japanese soldiers). In another study of Yoshimura, three groups of young males (16–17 year old) and adults were exposed to either 15 minutes daily immersion of the foot in ice water, 30 minutes immersion or no immersion (control group)

[75]. The authors reported that no changes occurred in the control group, but an enhanced hunting reaction was evident in the trained group, in particular the young boys. However, a closer look at the values in the Tables in [74] reveals that only the temperature response improved and not onset time of CIVD. This was followed by the acclimation study with the highest frequency, duration, and intensity of cold exposure by Adams and Smith [1]. Five subjects immersed their right index finger in ice water for 20 minutes, four to six times a day for a month. They observed significant improvements of the CIVD response: the cycle time decreased from 8.0 ± 0.2 minutes to 7.0 ± 0.2 minutes and the final finger temperature increased from 8.7 ± 0.5 to 12 ± 0.7°C. However, the longest acclimation protocol to date, consisting of 6 subjects immersing one finger in stirred water at 0°C six times a day for 125 consecutive days, found no differences in thermal responses between the immersed finger and contralateral, nontrained finger [22].

Twenty-First Century

Recently, a revived interest in CIVD trainability has led to several controlled studies on this topic. While the variation in training regimens and CIVD quantification continues to make it difficult to compare across studies, the general trend also appears to be minimal adaptation with laboratory acclimation programs. To determine the repeatability of CIVD, 21 subjects immersed their middle finger in 4°C water for 30 minutes for five consecutive days [59]. The CIVD appeared to be reproducible, which logically implies an absence of acclimation over these five days.

Extending training protocols to immersing the whole hand, a series of studies in our laboratory provided inconsistent evidence for thermal adaptation. Geurts *et al.* [36] investigated the trainability of CIVD in 11 subjects who immersed the left hand for 30 minutes in 8°C water 5 days/week for two weeks. No changes were observed in mean finger skin temperature during immersion over time and no difference existed with the right hand that was used as a control. In a similar study with an extended time period of three instead of two weeks, Geurts *et al.* [34] observed a reduction in mean finger skin temperature from 14.2 ± 1.9 to 11.7 ± 1.4°C. In contrast, Geurts *et al.* [35] reported a significant increase of about 2°C in index finger nail bed temperature after two weeks of daily immersion in 8°C water for 30 minutes. The immersion depth, water temperature, and measurement sites were identical for all three studies, and the authors could advance no suggestions for the large variability in overall responses across the three studies.

Using an immersion protocol similar to that of the series of studies by Geurts and colleagues except for temperature measurement at the finger pad of all digits, Mekjavic *et al.* [55] invited nine subjects to immerse one hand 30 minutes daily in 8°C water for 13 days while the other hand served as a control. The number of CIVD waves as well as average finger temperature decreased for the immersed hand, and the same was observed in the contralateral hand, which was measured only before and after the 13 days (see Figure 4). Daanen *et al.* [18] also exposed one hand to cold and used the other as a control in 8 mountaineers. They immersed the hand in ice water for 15 minutes daily for 14 consecutive days. Similar to the observations of Mekjavic *et al.* [55], the mean finger skin temperature dropped due to training in both hands, in this case, by 3 to 4°C. Overall, the observed changes in both the trained and untrained hands point at an increase in sympathetic outflow resulting from the local cold exposure.

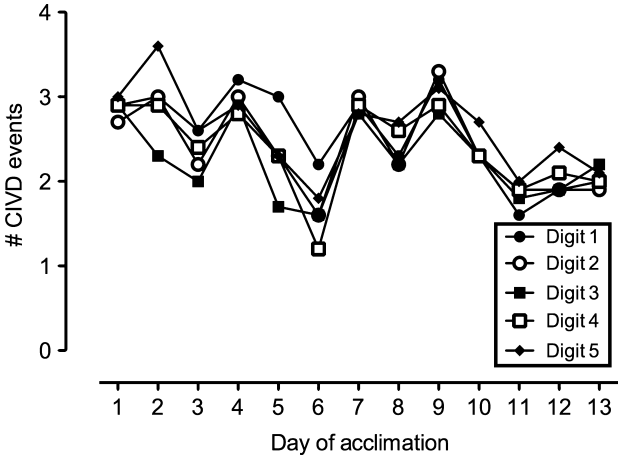

Figure 4. The frequency of CIVD events over 13 days of 30 minutes hand immersion in 8°C water, demonstrating a gradual decline in frequency in all digits. Data redrawn with permission from Mekjavic *et al.* [54].

Two studies on CIVD trainability focused on the foot. Savourey *et al.* [66] asked subjects to immerse the lower limbs up to 20 cm above the knees in 0–5°C water twice a day, 5 days/week for a month until the pain was no longer tolerable (approximately five minutes at the start of training and 60 minutes at the end of training) and found an increased mean foot temperature at the end of training. Unfortunately, other CIVD parameters were not reported. In a detailed analysis of CIVD trainability in the foot, Reynolds *et al.* [65] asked 10 subjects to immerse the left foot in 8°C water for 30 minutes, 5 days/week for three weeks. Overall, no changes were observed in foot temperature or any enhancement of CIVD (see Figure 5). Most of the times (86%), no CIVD of any kind (defined in that study as a 1°C rise in skin temperature) was observed in the toes, and the number of CIVD occurrences did not increase during the training. Also, the toe temperature at the end of the immersion period did not change over the 15 days.

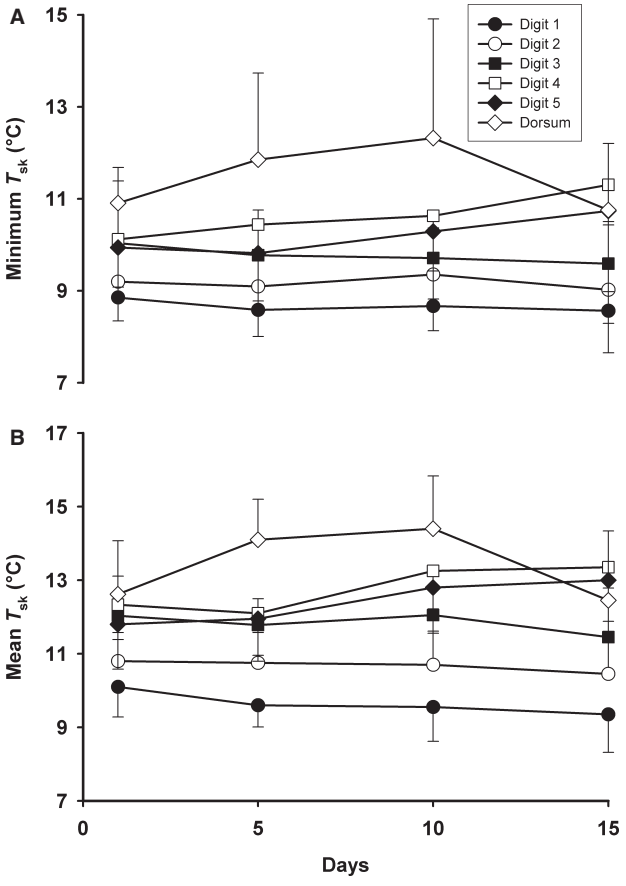

Figure 5. Minimum (**A**) and mean (**B**) skin temperature values for the five digits and the dorsum of the left foot at days 1, 5, 10, and 15 of acclimation, demonstrating minimal changes. From Reynolds *et al.* [64] with permission.

Conclusions Regarding Laboratory Studies

Table 1 shows an overview of the main field and laboratory studies previously discussed. In surveying laboratory-based attempts at eliciting cold adaptations in the extremities, only one laboratory acclimation study reported clear evidence of CIVD trainability across a number of parameters [1]. Two other studies demonstrated moderate levels of trainability with higher peripheral temperatures [35,66], whereas Yoshimura [75] found some evidence for trainability in youngsters only. In contrast, many studies found no effect of repeated immersions [22,36,37,59,65]. Furthermore, three studies observed a decrease in CIVD response after repeated cold exposure [18,34,55] and concluded that the extremities may actually be at a greater risk after training. Overall, although the general trend is for no laboratory-based acclimation, it remains difficult to account for the disparate and contradictory findings across studies.

It can be argued that the nonsignificant reports resulted from an acclimation protocol that was inadequate in intensity, duration, or frequency of cold exposure. Four daily immersions of the index finger in ice water for a month elicited faster onset of CIVD and a decrease in pain in the index finger compared with nontrained digits [1]. In contrast, in most recent studies, the subjects immersed their extremity only once every day, whereas older studies performed six immersions daily [22,37]. Few studies can logistically replicate the four 20-minute daily immersions over a month performed by Adams and Smith [1], and such an intensive protocol may not be practical to implement. More importantly, a prolonged laboratory acclimation regimen does not appear to guarantee thermal adaptations in the extremities, as the most extensive protocol achieved to date, that of six daily immersions for 125 days, observed no trainability in thermal responses [22].

Variability in water temperature and depth of immersion can also potentially influence the presence or magnitude of thermal adaptation. A larger cooled surface area may relate to a greater cold stimulus, and thus increase trainability. Conversely, from previous studies of Sendowski *et al.* [68], it is proposed that deeper immersion also causes cooling of the supplying blood vessels and thus may inhibit CIVD magnitude. Current data from trainability studies favor the former perspective, as Reynolds *et al.* [65] reported no thermal adaptations with foot immersion, whereas Savourey *et al.* [66] immersed the leg up to the knee in cold water and elicited higher foot temperatures after acclimation. While speculative, the small amount of exposed surface area may help explain the lack of thermal adaptation in many studies utilizing only finger immersion. The water temperature in most laboratory acclimation studies ranges from 0 to 8°C; generally, the older studies used ice water, as it is easy to control temperature at 0°C. Recent studies employ temperatures above 5°C as pain seems to be less, especially with immersion of the whole hand or foot rather than one finger [68]. However, the trainability of CIVD does not appear to be influenced by water temperature within the surveyed studies, as identical results of no CIVD trainability were found by Daanen *et al.* [18] and Mekjavic *et al.* [55] with water temperatures of 0°C and 8°C, respectively.

Potential Mechanisms for CIVD Adaptation

Despite >75 years of research, the actual physiological mechanisms underlying the CIVD response remain largely speculative, such that no clear model for either CIVD or its possible adaptation exists. The potential mechanisms for CIVD were last reviewed by Daanen [15], and included (1) axon reflexes, (2) dilating substances in the blood, (3) a blockade of the neuromuscular transmission between the sympathetic neurons and the AVAs, and (4) effects of cold on vascular smooth muscle activity. Recent reviews into the proposed mechanisms and modulators of cutaneous vasoconstriction and vasodilation of the extremities during cold

exposure can be found elsewhere [13,15,44]. Therefore, this section will only briefly review these mechanisms while focusing on what may be learnt from adaptation studies.

The oldest hypothesis comes from initial description of CIVD by Lewis [49]. He concluded from denervation experiments that an axon reflex had to be the primary cause for CIVD: impulses from receptive nerve endings of unmyelinated neurons in the skin inhibit the sympathetic nerve to the AVA and cause a relaxation. Daanen and Ducharme [17], however, were unable to evoke axon reflexes in a cold hand during the hunting reaction despite strong and painful stimulation of the skin. Therefore, the axon reflex hypothesis is an unlikely explanation of the CIVD response.

Some authors suppose that the AVA vasomotion is due to a dilating substance in the blood [4]. Cooling increases the release of NO, a powerful vasodilator in the endothelium of blood vessels, in cutaneous vessels of rabbit ears, but not in deep arteries, during cholinergic stimulation [24]. Also, cooling reduces the contraction to adrenergic activation in cutaneous vessels of rabbit ears [31]. More recently, Peltonen and Pyornila [61] observed a link between CIVD and NO concentration in birds. However, to our knowledge, the involvement of NO during CIVD has not yet been established in humans.

Another hypothesis is that the low tissue temperature results in a nervous blockade of the neuromuscular junction between the sympathetic nerve ending and the smooth muscle wall. This blockade may be due to a cessation of NE transmitter release [32], or an increased sensitivity of the α_2-receptors for NE in the cold [30] inducing a decrease in tissue temperature, which may become so low that a nervous blockade occurs. Finally, the release of the constrictive status of the AVA during CIVD may be the direct result of cold acting on the contractile elements in the smooth muscle [43].

It is undisputed that CIVD magnitude and onset time is also strongly dependent on central factors and sympathetic activity, which is clearly visible in the strong effect of manipulations in core temperature on the CIVD response [16,25,26,28]. Supporting evidence was found by Mekjavic *et al.* [55] in their finding that, after 15 days of immersing one hand in 8°C water, both the acclimated and contralateral (nonacclimated) hand demonstrated decreased CIVD frequency and finger temperatures. Such observations have resulted in an additional central model explaining CIVD, wherein the release of peripheral vasoconstriction serves to release excess heat from the body assuming sufficient body heat content in the core [25–27].

The most likely explanation of CIVD is probably a combination of vasodilators released in cold tissue, a neuromuscular blockade at the sympathetic nerve/AVA junction and direct effect of cold on the contractile mechanism of the AVA. Overall, this lack of consensus makes it difficult to speculate on the potential mechanisms that may be responsible for an enhanced CIVD response with repeated cold exposure. However, initial work is starting to explore the effects of repeated cold exposure on sympathetic drive and also blood-borne dilatory substances.

Changes in sympathetic outflow over time may contribute to CIVD adaptation, as the repeated immersions should result in a reduced sympathetic outflow over time [46,66]. Many authors reported a decrease in pain or subjective thermal discomfort with repeated local cold exposure [18,22,36,67]. In turn, the reduced pain sensation amplifies the decrease in sympathetic outflow as pain activates the sympathetic system. The reduction in pain sensation may be caused by less sensory input, but is more likely caused by central nervous inhibition of the afferent sensory input. However, others have suggested that the stress of cold exposure causes an elevation in sympathetic activity, resulting in enhanced vasoconstrictory tone and negative adaptations to local cold acclimation [55]. Only one study measured blood values related to sympathetic outflow [35]. They found no changes in catecholamines over the acclimation protocol. However, as they also observed no changes in CIVD response, the potential role of these factors in any changes in finger thermal responses to repeated cold exposure remains inconclusive. The relative change in sympathetic/parasympathetic drive may be estimated using heart-rate variability measurements during repeated cold immersions of the hands but, to our knowledge, heart rate variability has not been employed in any CIVD study. It is recommended in future studies that sympathetic activity, whether directly through blood markers or indirectly via techniques, such as heart rate variability, be determined to verify the claims that the sympathetic system plays a role in trainability.

Endothelin-1, a potent vasoconstrictor peptide, was measured by Nakamura *et al.* [57] in control individuals, along with individuals with Raynauds and also vibration-induced white finger. The authors reported that endothelin-1 levels were elevated rapidly upon finger cold immersion in both control and Raynauds individuals. In Raynauds, this rise was much higher, and it remained elevated even after immersion. However, there was no correlation between endothelin-1 levels and incidences of CIVD, suggesting that, while endothelin-1 is highly related to sympathetic hyperactivity, it does not directly contribute to the opening of peripheral blood vessels eliciting CIVD [57]. Geurts *et al.* [35] observed no changes in either endothelin-1 or NO levels in response to repeated hand immersions, but the caveat of no thermal acclimation precluded any conclusions.

CONCLUSIONS AND RECOMMENDATIONS

Overall, while broad improvements in thermal responses in individuals who live or work in cold environments are possible, microcirculatory adaptations and changes in the CIVD response in the fingers and toes appear to be neither guaranteed nor predictable. Much of the evidence for adaptation has involved cross-sectional studies, but significant gaps remain in understanding the contribution of genetic or morphological differences across different ethnic populations in cold response, along with the role of self-selection when considering comparisons across different occupations. The primary systematic improvement with prolonged acclimation is in a decreased perceptual discomfort or pain. However, with notable exceptions [1,63], longitudinal and laboratory studies have found minimal improvement in actual CIVD measures, with some finding that thermal responses actually became impaired over the acclimation period. Given the emphasis on developing strategies for protecting from cold injuries in occupational and recreational settings, people should not rely on physiological adaptation through repeated local cold exposure. Rather, given the importance of overall body thermal status on CIVD responses, individuals should try to keep their body core warm and wear well-insulated and well-fitted gloves and boots to prevent the occurrence of local cold injuries [9]. One avenue for further research appears to be in understanding the interactions between exercise and hypoxia on local blood flow and CIVD trainability. However, such research should be performed with standardized definitions for CIVD and its measurement rather than with the historic and current wide variability in methodology.

PERSPECTIVE

An enhanced circulation to the extremities is presumed to occur with repeated exposure to cold, serving as a protective mechanism against peripheral cold injury. However, systematic improvements in CIVD are neither guaranteed nor predictable, and individuals should not rely on improving peripheral cold tolerance through repeated cold exposure. The field is confused by a lack of standardization in definitions and methodology, and emphasis should be on investigating the underlying mechanisms behind peripheral blood flow changes with local cold exposure.

REFERENCES

1. Adams T, Smith RE. Effect of chronic local cold exposure on finger temperature responses. *J Appl Physiol* 17: 317–322, 1962.
2. Allen JA. The influence of physical conditions in the genesis of species. *Radical Rev* 1: 108–140, 1877.
3. Amon M. Effect of 'Sleep High-Train Low' Hypoxic Training on Cold Induced Vasodilatation (CIVD) Response in Fingers and Toes. Ljubljana: Jozef Stefan International Postgraduate School, 2009.
4. Aschoff J. Uber die kaltedilatation der extremitat des menschen in eiswasser. *Pflugers Archiv* 248: 183–196, 1944.
5. Astrand P-O, Rodahl K, Dahl HA, Stromme SB. Textbook of Work Physiology: Physiological Bases of Exercise. Champaign, IL: Human Kinetics, 2003, p. 411.
6. Baumhakel M, Bohm M. Recent achievements in the management of Raynaud's phenomenon. *Vasc Health Risk Manag* 6: 207–214, 2010.
7. Bergersen TK, Hisdal J, Walloe L. Perfusion of the human finger during cold-induced vasodilatation. *Am J Physiol* 276: R731–R737, 1999.
8. Brajkovic D, Ducharme MB. Facial cold-induced vasodilation and skin temperature during exposure to cold wind. *Eur J Appl Physiol* 96: 1–11, 2006.
9. Brajkovic D, Ducharme MB, Frim J. Relationship between body heat content and finger temperature during cold exposure. *J Appl Physiol* 90: 2445–2452, 2001.
10. Bridgman SA. Thermal status of Antarctic divers. *Aviat Space Environ Med* 61: 795–801, 1990.
11. Bridgman SA. Peripheral cold acclimatization in Antarctic SCUBA divers. *Aviat Space Environ Med* 62: 733–738, 1991.
12. Brown GM, Semple RE, Lennox CS, Bird GS, Baugh CW. Response to cold of Eskimos of the eastern Canadian Arctic. *J Appl Physiol* 18: 970–974, 1963.
13. Charkoudian N. Mechanisms and modifiers of reflex induced cutaneous vasodilation and vasoconstriction in humans. *J Appl Physiol* 109: 1221–1228, 2010.
14. Daanen HAM. Central and Peripheral Control Of Finger Blood Flow in the Cold. Amsterdam: VU University, 1997.
15. Daanen HA. Finger cold-induced vasodilation: a review. *Eur J Appl Physiol* 89: 411–426, 2003.
16. Daanen HA, Ducharme MB. Finger cold-induced vasodilation during mild hypothermia, hyperthermia and at thermoneutrality. *Aviat Space Environ Med* 70: 1206–1210, 1999.
17. Daanen HA, Ducharme MB. Axon reflexes in cold exposed fingers. *Eur J Appl Physiol* 81: 240–244, 2000.
18. Daanen HAM, Raymann RJ, Stroop M. Trainability of cold induced vasodilation. In: 12th International Conference on Environmental Ergonomics, edited by Mekjavic IB, Kounalakis SN, Taylor NAS. Piran, Slovenia: International Society for Environmental Ergonomics, 2007, p. 317–319.
19. Daanen HA, Van de Linde FJ, Romet TT, Ducharme MB. The effect of body temperature on the hunting response of the middle finger skin temperature. *Eur J Appl Physiol Occup Physiol* 76: 538–543, 1997.
20. Daanen HA, van der Struijs NR. Resistance Index of Frostbite as a predictor of cold injury in Arctic operations. *Aviat Space Environ Med* 76: 1119–1122, 2005.
21. Daanen HA, van Ruiten HJ. Cold-induced peripheral vasodilation at high altitudes—a field study. *High Alt Med Biol* 1: 323–329, 2000.
22. Eagan CJ. Unilateral cold-adaptation to recurrent ice-water immersion. *Physiologist* 3: 51, 1960.
23. Felicijan A, Golja P, Milcinski M, Cheung SS, Mekjavic IB. Enhancement of cold-induced vasodilatation following acclimatization to altitude. *Eur J Appl Physiol* 104: 201–206, 2008.
24. Fernandez N, Monge L, Garcia-Villalon AL, Garcia JL, Gomez B, Dieguez G. Cooling effects on nitric oxide production by rabbit ear and femoral arteries during cholinergic stimulation. *Br J Pharmacol* 113: 550–554, 1994.

25. Flouris AD, Cheung SS. Influence of thermal balance on cold-induced vasodilation. *J Appl Physiol* 106: 1264–1271, 2009.
26. Flouris AD, Cheung SS. Thermal basis of finger blood flow adaptations during abrupt perturbations in thermal homeostasis. *Microcirculation* 18: 56–62, 2011.
27. Flouris AD, Cheung SS, Fowles JR, Kruisselbrink LD, Westwood DA, Carrillo AE, Murphy RJ. Influence of body heat content on hand function during prolonged cold exposures. *J Appl Physiol* 101: 802–808, 2006.
28. Flouris AD, Westwood DA, Mekjavic IB, Cheung SS. Effect of body temperature on cold induced vasodilation. *Eur J Appl Physiol* 104: 491–499, 2008.
29. Fox RH, Wyatt HT. Cold-induced vasodilatation in various areas of the body surface of man. *J Physiol* 162: 289–297, 1962.
30. Freedman RR, Sabharwal SC, Moten M, Migaly P. Local temperature modulates alpha 1- and alpha 2-adrenergic vasoconstriction in men. *Am J Physiol* 263: H1197–H1200, 1992.
31. Garcia-Villalon AL, Monge L, Montoya JJ, Garcia JL, Fernandez N, Gomez B, Dieguez G. Cooling and response to adrenoceptor agonists of rabbit ear and femoral artery: role of the endothelium. *Br J Pharmacol* 106: 727–732, 1992.
32. Gardner CA, Webb RC. Cold-induced vasodilatation in isolated, perfused rat tail artery. *Am J Physiol* 251: H176–H181, 1986.
33. Geurts CL, Sleivert GG, Cheung SS. Effect of cold-induced vasodilatation in the index finger on temperature and contractile characteristics of the first dorsal interosseus muscle during cold-water immersion. *Eur J Appl Physiol* 93: 524–529, 2005.
34. Geurts CL, Sleivert GG, Cheung SS. Local cold acclimation of the hand impairs thermal responses of the finger without improving hand neuromuscular function. *Acta Physiol Scand* 183: 117–124, 2005.
35. Geurts CL, Sleivert GG, Cheung SS. Central and peripheral factors in thermal, neuromuscular, and perceptual adaptation of the hand to repeated cold exposures. *Appl Physiol Nutr Metab* 31: 110–117, 2006.
36. Geurts CL, Sleivert GG, Cheung SS. Local cold acclimation during exercise and its effect on neuromuscular function of the hand. *Appl Physiol Nutr Metab* 31: 717–725, 2006.
37. Glaser EM, Whittow GC. Retention in a warm environment of adaptation to localized cooling. *J Physiol* 136: 98–111, 1957.
38. Greenfield AD, Kernohan GA, Marshall RJ, Shepherd JT, Whelan RF. Heat loss from toes and fore-feet during immersion in cold water. *J Appl Physiol* 4: 37–45, 1951.
39. Hale AR, Burch GE. The arteriovenous anastomoses and blood vessels of the human finger. Morphological and functional aspects. *Medicine (Baltimore)* 39: 191–240, 1960.
40. Hellstrom B, Andersen KL. Heat output in the cold from hands of Arctic fishermen. *J Appl Physiol* 15: 771–775, 1960.
41. Jobe JB, Goldman RF, Beetham WP Jr. Comparison of the hunting reaction in normals and individuals with Raynaud's disease. *Aviat Space Environ Med* 56: 568–571, 1985.
42. Jobe JB, Sampson JB, Roberts DE, Kelly JA. Comparison of behavioral treatments for Raynaud's disease. *J Behav Med* 9: 89–96, 1986.
43. Keatinge WR, Harman MC. Local mechanisms controlling blood vessels. In: Monographs of the Physiological Society. London: Academic Press, 1980.
44. Kellogg DL Jr. In vivo mechanisms of cutaneous vasodilation and vasoconstriction in humans during thermoregulatory challenges. *J Appl Physiol* 100: 1709–1718, 2006.
45. Krog J, Folkow B, Fox RH, Andersen KL. Hand circulation in the cold of Lapps and North Norwegian fisherman. *J Appl Physiol* 15: 654–658, 1960.
46. LeBlanc J, Dulac S, Cote J, Girard B. Autonomic nervous system and adaptation to cold in man. *J Appl Physiol* 39: 181–186, 1975.
47. Leblanc J, Hildes JA, Heroux O. Tolerance of Gaspe fishermen to cold water. *J Appl Physiol* 15: 1031–1034, 1960.
48. Lewin R, Foley R. Principles of Human Evolution. Malden, MA: Blackwell Science Ltd., 2004.
49. Lewis T. Observations upon the reactions of the vessels of the human skin to cold. *Heart* 15: 177–208, 1930.
50. Livingstone SD. Changes in cold-induced vasodilation during Arctic exercises. *J Appl Physiol* 40: 455–457, 1976.
51. Livingstone SD, Romet T, Keefe AA, Nolan RW. Changes in cold tolerance due to a 14-day stay in the Canadian Arctic. *Int J Biometeorol* 39: 182–186, 1996.
52. Mathew L, Purkayastha SS, Jayashankar A, Sharma RP. Responses of high altitude natives a standard cold test at sea level. *Aviat Space Environ Med* 50: 372–375, 1979.
53. Mathew L, Purkayastha SS, Selvamurthy W, Malhotra MS. Cold-induced vasodilatation and peripheral blood flow under local cold stress in man at altitude. *Aviat Space Environ Med* 48: 497–500, 1977.
54. Meehan JP. Individual and racial variations in a vascular response to a cold stimulus. *Mil Med* 116: 330–334, 1955.
55. Mekjavic IB, Dobnikar U, Kounalakis SN, Musizza B, Cheung SS. The trainability and contralateral response of cold-induced vasodilatation in the fingers following repeated cold exposure. *Eur J Appl Physiol* 104: 193–199, 2008.
56. Miller LK, Irving L. Local reactions to air cooling in an Eskimo population. *J Appl Physiol* 17: 449–455, 1962.
57. Nakamura H, Matsuzaki I, Hatta K, Nagase H, Nobokuni Y, Kambayashi Y, Ogino K. Blood endothelin-1 and cold-induced vasodilation in patients with primary Raynauld's phenomenon and workers with vibration-induced white finger. *Inter Angiol* 22: 243–249, 2003.
58. Nelms JD, Soper DJ. Cold vasodilatation and cold acclimatization in the hands of British fish filleters. *J Appl Physiol* 17: 444–448, 1962.
59. O'Brien C. Reproducibility of the cold-induced vasodilation response in the human finger. *J Appl Physiol* 98: 1334–1340, 2005.
60. O'Brien C, Castellani JW, Sawka MN. Thermal face protection delays finger cooling and improves thermal comfort during cold air exposure. *Eur J Appl Physiol*, in press (April 3, 2011).
61. Peltonen LM, Pyornila A. Local action of exogenous nitric oxide (NO) on the skin blood flow of rock pigeons (*Columba livia*) is affected by acclimation and skin site. *J Exp Biol* 207: 2611–2619, 2004.
62. Purkayastha SS, Ilavazhagan G, Ray US, Selvamurthy W. Responses of Arctic and tropical men to a standard cold test and peripheral vascular responses to local cold stress in the Arctic. *Aviat Space Environ Med* 64: 1113–1119, 1993.
63. Purkayastha SS, Selvamurthy W, Ilavazhagan G. Peripheral vascular response to local cold stress of tropical men during sojourn in the Arctic cold region. *Jpn J Physiol* 42: 877–889, 1992.
64. Purkayastha SS, Sharma RP, Ilavazhagan G, Sridharan K, Ranganathan S, Selvamurthy W. Effect of vitamin C and E in modulating peripheral vascular response to local cold stimulus in man at high altitude. *Jpn J Physiol* 49: 159–167, 1999.
65. Reynolds LF, Mekjavic IB, Cheung SS. Cold-induced vasodilatation in the foot is not homogenous or trainable over

repeated cold exposure. *Eur J Appl Physiol* 102: 73–78, 2007.
66. Savourey G, Barnavol B, Caravel JP, Feuerstein C, Bittel JH. Hypothermic general cold adaptation induced by local cold acclimation. *Eur J Appl Physiol* 73: 237–244, 1996.
67. Sawada S, Araki S, Yokoyama K. Changes in cold-induced vasodilatation, pain and cold sensation in fingers caused by repeated finger cooling in a cool environment. *Ind Health* 38: 79–86, 2000.
68. Sendowski I, Savourey G, Besnard Y, Bittel J. Cold induced vasodilatation and cardiovascular responses in humans during cold water immersion of various upper limb areas. *Eur J Appl Physiol Occup Physiol* 75: 471–477, 1997.
69. Shitzer A, Stroschein LA, Gonzalez RR, Pandolf KB. Lumped-parameter tissue temperature-blood perfusion model of a cold-stressed fingertip. *J Appl Physiol* 80: 1829–1834, 1996.
70. Simmons GH, Barrett-O'Keefe Z, Minson CT, Halliwill JR. Cutaneous vascular and core temperature responses to sustained cold exposure in hypoxia. *Exp Physiol*, in press (June 24, 2011).
71. Simmons GH, Fieger SM, Minson CT, Halliwill JR. Hypoxic cutaneous vasodilation is sustained during brief cold stress and is not affected by changes in CO_2. *J Appl Physiol* 108: 788–792, 2010.
72. Simmons GH, Fieger SM, Wong BJ, Minson CT, Halliwill JR. No effect of systemic isocapnic hypoxia on alpha-adrenergic vasoconstrictor responsiveness in human skin. *Acta Physiol (Oxf)* 201: 339–347, 2011.
73. Spealman CR. Effect of ambient air temperature and of hand temperature on blood flow in hands. *Am J Physiol* 145: 218–222, 1945.
74. Wilson O, Goldman RF. Role of air temperature and wind in the time necessary for a finger to freeze. *J Appl Physiol* 29: 658–664, 1970.
75. Yoshimura H. Acclimatization to heat and cold. In: Essential Problems in Climatic Physiology, edited by Yoshimura H, Ogata K, Itoh S. Tokyo: Nankodo Ltd., 1960, p. 61–75.
76. Yoshimura H, Iida T. Studies on the reactivity of skin vessels to extreme cold. Part 1. A point test on the resistance against frostbite. *Jpn J Physiol* 1: 147–159, 1950.
77. Yoshimura H, Iida T. Studies on the reactivity of skin vessels to extreme cold II. Factors governing the individual difference of the reactivity, or the resistance against frostbite. *Jpn J Physiol* 2: 177–185, 1952.